## A Case of *Corynebacterium pseudodiphtheriticum* Nosocomial Pneumonia

**To the Editor:** *Corynebacterium pseudodiphtheriticum* has seldom been isolated from patients with upper respiratory tract infections and pneumonia. Most reported infections are community acquired and occur in patients with underlying disease and immunosuppression (1). We report a case characterized by hospital-acquired pneumonia in a debilitated patient. Review of the literature indicates that *C. pseudodiphtheriticum* should be regarded an emerging pathogen.

On April 1, 1998, a 68-year-old woman was admitted to the intensive care unit for acute respiratory distress. She had a 14-month history of amyotrophic lateral sclerosis. Three weeks before admission, she had been hospitalized for *Staphylococcus aureus* pneumonia and had recovered after treatment with amoxicillin and clavulanic acid plus ciprofloxacin. At the time of admission, the patient had a temperature of 38°C. Systolic blood pressure was 120 mm Hg. Ventilation was spontaneous, with respirations 24 per minute; pulmonary sibilants were noted. Respiratory acidosis was also identified, with a pH of 7.35, SaO2 92%, PaO2 60 mm Hg, and PaCO2 60 mm Hg. Laboratory data included 18,000 leukocytes per ml (90% polymorphonuclear cells) and a serum fibrin level of 7 g/L. A chest X-ray showed pneumopathy of the lower segment of the right lung, which was compatible with the diagnosis of inhalation pneumopathy. On day 2 of admission, the patient's temperature was 39°C, and she had paresis of the vocal cords. After *C. pseudodiphtheriticum* infection was diagnosed, treatment with intravenous cloxacillin (l g 3 times/day) and amoxicillin plus clavulanic acid (l g 3 times/day) was started. On day 3 after admission, the patient's breathing worsened, a radiograph showed bilateral pneumopathy, and she was intubated for mechanical ventilation. Two days later, her breathing improved, and a second bronchic aspiration was sterile. The patient eventually died of unrelated complications.

Direct microscopy examination of a Gram-stained bronchial aspiration sample showed numerous polymorphonuclear cells and gram-positive bacilli in parallel rows, which did not show pleomorphism. After 48 hours of incubation at 37°C, $10^6$ colony-forming units/ml of a coryneform bacillus further identified as *C. pseudodiphtheriticum* grew in pure culture on blood agar gelose (BioMérieux, La Balme les Grottes, France) under a 5% $CO_2$ atmosphere and did not produce hemolysis. The test for catalase was positive, and the following biochemical characteristics were obtained by using a commercial identification strip (ApiCoryne, BioMérieux): absence of carbohydrate fermentation, urea hydrolysis, and nitrate reduction compatible with C. *pseudodiphtheriticum*. Minimum inhibitory concentrations (disk diffusion method) were 2 mg/L for amoxicillin, 2 mg/L for cefalotin, 0.09 mg/L for doxycycline, 0.03 mg/L for gentamicin, <4 mg/L for vancomycin, 16 mg/L for erythromycin, and 20 mg/L for trimethoprim-sulfamethoxazole. Identification was confirmed by analysis of the cell-wall fatty acid profile by the Sherlock system, by the trypticase soy broth agar database 3.9 (MIDI Inc., Newark, DE), and by 16S rRNA sequence analysis under previously described conditions (2). The 16S rRNA gene sequence was compared with all eubacterial 16S rRNA sequences available in the GenBank database by using the multisequence comparison Advanced Blast NCBI. The sequence had a 99% similarity to that of *C. pseudodiphtheriticum* (1039/1047 base pairs).

Eighty-nine cases of infection possibly caused by *C. pseudodiphtheriticum* have been identified in the last 57 years. Of these, 57 (62.9%) were upper respiratory infections, which included rhinosinusitis, tracheitis, tracheobronchitis, and bronchitis; 19 (21.3%) were pneumonia (3-7). Ten (11.2%) cases of endocarditis were reported (8); there was also one case each of urinary tract malakoplakia after renal transplantation (9), lung abcess (10), diskitis (11), and lymphadenitis (12).

Unlike *C. diphtheriae, C. pseudodiphtheriticum* is a commensal bacterium that does not produce toxins and needs predisposing factors to become a pathogen causing pneumonia. Of patients with hospital-acquired *C. pseudodiphtheriticum* upper respiratory tract infections and pneumonia (7 of 26 upper respiratory tract infections and 2 of 14 cases of pneumonia reported in the early 1990s), all had underlying pathologic features. Predisposing factors were as follows: 33.7% had lung and tracheobronchial diseases, including chronic obstructive pulmonary disease, angina

(5), chronic emphysema, asthma, and bronchitis (6); 32.5% had congestive heart failure (5). Of those with immunodepression, 5% had AIDS, 7.2% had undergone chemotherapy or prolonged steroid use; and 18.2% had other pathologic features, disseminated intravascular coagulation (6), chronic renal failure, diabetes mellitus (5), and connective tissue disease (5,6).

The first source of pneumonia is usually inhalation, as was the case for our patient, who had paresis of the vocal cords. She was not immunosuppressed but was debilitated by amyotrophic lateral sclerosis. The second factor is often an endotracheal intubation, as reported in a previously healthy 29-year-old trauma victim who contracted pneumonia due to *C. pseudodiphtheriticum* after 7 days of intubation (7). An increase in cases reported from 1932 to 1998 indicates the emergence of infections due to *C. pseudodiphtheriticum*. Thirty-four cases were reported from 1932 to 1989 (57 years), and 55 cases were reported from 1990 to 1998 (8 years). Reasons for the emergence of *C. pseudodiphtheriticum* infections may include confusion between *C. diphtheriae* and *C. pseudodiphtheriticum* infections. For example, two cases of *C. pseudodiphtheriticum* exudative upper respiratory tract infections with a pseudomembrane were first diagnosed as respiratory diphtheria. In the first case, *C. pseudodiphtheriticum* was isolated from a 32-year-old Uzbek man who had a severe sore throat and dysphagia lasting 2 days (3). In a second case, a 4-year-old girl had exudative pharyngitis with a pseudomembrane, which was possibly caused by *C. pseudodiphtheriticum* (4). The availability of commercial strips for the identification of *C. pseudodiphtheriticum* and 16S rRNA sequencing eliminates such confusion.

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## Family Outbreak of *Rickettsia conorii* Infection

**To the Editor:** Over a 15-day period, three young siblings were separately taken to an emergency room in Israel, with symptoms suggesting a contagious viral illness (fever, maculopapular rash, hepatosplenomegaly, lymphadenopathy, neutropenia, and thrombocytopenia). None of the children had been in direct contact with animals. Specific immunoglobulin (IgM) immunofluorescence assay (IFA) 7 to 8 days after admission of each child confirmed the diagnosis of *Rickettsia conorii* infection.

Spotted fever is the generic name given to a variety of tickborne rickettsial diseases distributed worldwide. In Mediterranean countries, including Israel, spotted fever is caused by members of the *R. conorii* complex. Spotted fever has been endemic in Israel for more than 40 years, with several hundred cases reported annually. In 1997, two fatal cases were reported

(1). Spotted fever is caused by a variant member of *R. conorii,* which is transmitted by the dog tick *Rhipicephalus sanguineous* (2,3). The disease has a broad spectrum of clinical signs, from asymptomatic to fatal (4,5). Symptoms and signs include fever, headache, vomiting, myalgia, conjunctivitis, and a typical maculopapular or purpuric rash. The tache noir at the site of the tick bite, which is found in patients in Europe, is seldom, if ever, seen in Israel.

The first patient, a 6-year-old boy, was taken to the pediatric emergency room with high fever and a diffuse rash, approximately 1 week after visiting a cousin who had similar complaints. Physical examination showed temperature of 40°C, chills, diffuse maculopapular rash all over the body, including the hands and feet, hepatosplenomegaly, and lymphadenopathy. Blood tests showed neutropenia, thrombocytopenia, and hyponatremia. Because *Rickettsia* was included in the differential diagnosis, immunofluorescent assay (IFA) for *Rickettsia* was performed and intravenous doxycycline (2 mg/kg/day) was initiated. One week later, the boy's 8-month-old sister was brought to the emergency room with similar complaints, and 2 days afterwards his 2-year-old sister began to have the same symptoms. A detailed history revealed that all children had played on a lawn frequented by dogs.

All three siblings had fever, chills, and diffuse maculopapular rash all over the body, including the hands and feet. An IgM IFA test for *R. conorii* from the first child was negative on the day of admission and became positive 8 days later. On the day of the boy's hospital discharge, his 8-month-old sister was taken to the emergency room. Her serology test was negative on admission but became positive 7 days later. The third (2-year-old) sibling's first blood test was negative, and the family did not agree to a second blood test. All three children responded well to doxycycline (2 mg/kg/day, with a double dose the first day) for 5 to 7 days. Most symptoms subsided within 48 hours.

Spotted fever is usually a sporadic illness and is not spread from person to person. Clusters of cases have been reported. Yagupsky reported spotted fever in Israel in a few children living near each other in an agricultural settlement (6). A report from the Delaware Division of Public Health described a group of children who had been camping together where contact with ticks was likely (7). This case illustrates that spotted fever may be acquired even without direct contact with animals, through exposure to ticks in places frequented by infected animals. Our report suggests that Rickettsial illness should be considered in the differential diagnosis of fever with rash in disease-endemic areas, even if the timing of similar complaints in several family members suggests a contagious viral illness.

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## Iron and the Role of *Chlamydia pneumoniae* in Heart Disease

**To the Editor:** Chronic infection of the coronary arteries by *Chlamydia pneumoniae* has been proposed as a heart disease risk factor (1). One reason for this proposal is the organism's association with one or more other risk factors for heart disease (2). However, an independent pathogenic role for *C. pneumoniae* in heart disease is unlikely if its presence is only a marker for another risk factor. In the Helsinki Heart Study (3), markers of chronic *C. pneumoniae* infection were a significant risk factor for a cardiac event, independent of most traditional

risk factors; however, some association with known risk factors was seen, including a positive association with smoking and an unexpected negative association with spare-time physical activity.

We postulate a key role for iron, a proposed risk factor for heart disease (4-6), in promoting the growth of *C. pneumoniae* in coronary arteries. Iron is an essential growth factor for nearly all pathogenic microorganisms (7). In particular, the growth of *C. pneumoniae* in a human lung cell line and in Hep-2 cells is strongly inhibited by iron restriction or by use of the iron chelator deferoxamine (8, P. Saikku, pers. comm.). Excess iron is present in atherosclerotic lesions. Seven times more iron is present in atherosclerotic than in healthy arteries (9).

Among proposed risk factors for heart disease, iron provides the most conceptually straightforward explanation for the presence of *C. pneumoniae* in coronary vessels. We propose that chronic infection of coronary arteries by *C. pneumoniae* occurs only if excess iron is present in vivo. Excess iron is defined as stored iron or iron in excess of the amount needed to maximize hematocrit. This implies that *C. pneumoniae* can establish infection in the coronary arteries only if a threshold level of available iron is present. Confirmation of the hypothesis could explain an association of *C. pneumoniae* with coronary atherosclerosis and, more generally, with ischemic heart disease and would be consistent with the greater susceptibility of men than women to *C. pneumoniae* infection (2) and myocardial infarction. Moreover, confirmation of the hypothesis would leave open the question of whether *C. pneumoniae* is directly atherogenic or merely finds fertile ground for growth in arteries because of the presence of iron above some threshold level.

Until age 20, men and women show few differences in prevalence of antibody titers against *C. pneumoniae*. After age 20, the prevalence of markers diverges sharply, with men showing a much steeper rise than women. This is similar to the patterns observed for both stored iron levels and rate of myocardial infarction in men and women, especially between the ages of 20 and 50 years (4,5). In later years, prevalence rates for *C. pneumoniae* markers do not rise as steeply for women as the curves for stored iron level or myocardial infarction rates (2). These patterns are compatible with associations between stored iron, myocardial infarction rate, and markers for infection with *C. pneumoniae*. Another relevant observation is the negative association of markers with spare-time physical activity (2). Such activity is associated with lower stored iron levels (10), which may decrease vulnerability to *C. pneumoniae*.

The presence of excess iron in regulating susceptibility to *C. pneumoniae* does not readily explain the geographic gradient in the frequency of antibodies (2). *C. pneumoniae* infection seems to be more prevalent near the equator. In general, acquisition of stored iron is more problematic among impoverished persons, many of whom live near the equator. Parasitic infections that cause chronic iron loss from bleeding in the gut and bladder, along with limited availability of easily absorbed heme iron in meat, tend to minimize iron acquisition in these areas. *C. pneumoniae* may be endemic in populations near the equator, especially among children in tropical urban slums, because of other factors that eliminate any differential effects on the basis of iron levels. In these areas chlamydial antibodies may be a good marker for invasion but not necessarily for disease.

We suggest that, above a modest threshold level of stored iron in vivo, *C. pneumoniae* acquires the ability to colonize coronary arteries. Invasion and colonization by the organism in vivo probably require a concentration of available iron similar to that needed for growth in cell culture. Even in a state of total iron depletion, iron is still present in the body in abundance. However, in iron depletion virtually all iron in the body is functional iron. Functional iron, i.e., iron in hemoglobin, may not be readily accessible to the organism. Our hypothesis implies that stored iron can be mobilized by *C. pneumoniae* for growth. An approach to testing the hypothesis would involve comparing the ability of *C. pneumoniae* to colonize macrophages from stored iron-replete persons with those from persons without stored iron. If the hypothesis is confirmed, maintenance of an iron-depleted state under medical supervision could be recommended as a preventive strategy against recolonization after a course of antibiotic therapy.

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## Filth Flies Are Transport Hosts of *Cryptosporidium parvum*

**To the Editor:** Infection with *Cryptosporidium parvum,* a zoonotic and anthroponotic coccidian parasite (1), may be fatal for persons with impaired immune systems (2), for whom a low number of oocysts can initiate life-threatening diarrhea (1). Insects such as promiscuous-landing synanthropic flies (i.e., coprophilic filth flies) are recognized transport hosts for a variety of parasites (3-5), but not for *C. parvum*. We assessed the role of synanthropic flies in the mechanical transmission of *C. parvum* oocysts.

Bovine diarrheic feces (20-ml specimens) containing 2.0 x $10^5$ oocysts/ml were placed in petri dishes in each of five 4-liter paper cages with approximately 250 pupae of laboratory-reared house flies (*Musca domestica* F58WTZ strain). Three days after the flies emerged, fecal specimens were collected on glass microscope slides placed in each cage. Thirty flies aspirated from each cage on days 3, 5, 7, 9, and 11 after emergence were eluted, and the eluants were processed by the cellulose acetate membrane (CAM)-filter dissolution method (6). Digestive tracts dissected from randomly selected flies and the glass slides with fly excreta were examined by immunofluorescent antibody (IFA) (7), and *C. parvum* oocysts were counted (8). Maggots of *M. domestica* were reared in fly larvae medium (PMI FEEDS, Inc., St. Louis, MO) contaminated with calf diarrheic feces (50 ml) containing 2.0 x $10^5$ *C. parvum* oocysts/ml. Resulting pupae were eluted, the eluants were processed by the CAM-filter dissolution method (6), and *C. parvum* oocysts were identified by IFA (7) and counted (8). Diarrheic fecal specimens from a *C. parvum*-uninfected calf were used as negative controls in similar experiments. Randomly selected samples containing fly-derived *C. parvum* oocysts were processed with acid-fast stain (AFS) (8) to check for normal cellular morphologic features.

Ten Victor-type flying-insect traps (Woodstream, Lititz, PA) were baited with rotten fish and placed inside a barn (approximately 880 $m^2$) in which a male Holstein calf infected with *C. parvum* (AUCP-1 strain) was housed. The traps were emptied weekly, the flies were counted and identified (5,9), and the inside surfaces of the traps (containing fly excreta), along with the flies, were eluted with 200 ml of eluting fluid (6). The eluting fluid was filtered through a CAM (Millipore, Bedford, MA) (6,8), which was then processed (6), and *C. parvum* oocysts were identified by IFA (7) and counted (8).

The mean number of *C. parvum* oocysts per droplet of *M. domestica* was 4 to 20 (mean 7.0 $\pm$ 3.2), and the number of droplets increased over time. All flies harbored *C. parvum* oocysts on their external surfaces. On average, 14.0 + 6.8 fly excreta were counted per 1.0 $cm^2$ of glass slide. From 1 to 8 *C. parvum* oocysts were

detected in digestive tracts of flies exposed to feces with oocysts. *C. parvum* oocysts were also numerous on maggot and pupa surfaces; approximately 150 and 320 oocysts were recovered per maggot and pupa, respectively.

Wild-caught flies belonged to the families *Calliphoridae* (96% of total flies), *Sarcophagidae* (2%), and *Muscidae* (2%). An average of eight flies was caught per trap, and more than 90% of flies harbored *C. parvum* oocysts. The number of trap-recovered *C. parvum* oocysts per fly was 2 to 246 (mean 73 oocysts per fly).

Synanthropic flies that breed in or come in contact with a fecal substrate contaminated with *C. parvum* oocysts can harbor these oocysts both externally and internally and will mechanically deposit them on other surfaces. Therefore, synanthropic flies can serve as mechanical vectors for *C. parvum* oocysts and under poor sanitary conditions could be involved in the transmission of human and animal cryptosporidiosis. The biology and ecology of synanthropic flies indicate that their potential for mechanical transmission of *C. parvum* oocysts can be high. The morphologic and AFS and IFA staining characteristics of *C. parvum* oocysts recovered from the exoskeletons of flies and identified in their fecal spots suggest that oocysts are still viable.

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## The Cost-Effectiveness of Vaccinating against Lyme Disease

**To the Editor:** The recent article by Meltzer and colleagues (1) is an important contribution to a pertinent public health issue: who should receive the newly licensed Lyme disease vaccine. Answering this question is a daunting task, given the scarcity of valid data. Estimates of the spectrum and prevalence of the long-term sequelae of Lyme disease remain controversial (2-4). In generating their cost-effectiveness model, Meltzer et al. examined the cost savings involved in preventing three categories of classic organ-specific Lyme disease sequelae (cardiovascular, neurologic, and arthritic); however, they did not take into account the potential cost savings from preventing cases of a generalized symptom complex known as post-Lyme syndrome, which includes persisting myalgia, arthralgia, headache, fatigue, and neurocognitive deficits. These generalized sequelae, which are recognized by the National Institutes of Health as late sequelae of Lyme disease, have been found to persist for years after antibiotic therapy (5,6). Two population-based retrospective cohort studies (7,8) among Lyme disease patients whose illness was diagnosed in the mid-1980s determined that one third to half had clinically corroborated post-Lyme syndrome symptoms years after the initial onset of disease. Although these studies were conducted 15 years ago, when optimal antibiotic regimen guidelines were still evolving, the estimated cost of averting these often-disabling nonorgan-specific symptoms should also be taken into account in estimated

sensitivity analyses of vaccine cost-effectiveness. The cost of treating sequelae is weighted heavily in the cost-effectiveness models presented by Meltzer and colleagues, which adds importance to considering post-Lyme syndrome. Nevertheless, we recognize the difficulty of this modeling, especially in the absence of validated cost-of-treatment data for these generalized symptoms.

A point of correction is that Meltzer et al. erroneously cite one of these studies (7) to infer that the long-term clinical sequelae of Lyme disease lasted a mean of 6.2 years from the onset of disease. In this retrospective study, Shadick et al. evaluated 38 persons with a clinical history of Lyme disease a mean of 6.2 years from the onset of disease regardless of the presence of persisting symptoms; 25 of these patients had no residual symptoms at follow-up. To accurately estimate the duration of clinical sequelae, longitudinal evaluations of representative populations of Lyme disease patients will be required because late manifestations have been demonstrated months to years after diagnosis (9,10).

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